Pro-saccades predict cognitive decline in Parkinson's disease: ICICLE-PD

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Abstract

Objectives

Cumulative dementia incidence in Parkinson's disease (PD) is significant, with major personal and socioeconomic impacts upon individuals with PD and their carers. Early identification of dementia risk is vital to ensure optimal intervention. Saccadic deficits often distinguish neurodegenerative disorders and cognitive impairment, but their ability to predict cognitive decline in PD has yet to be determined.

Study aims: 1) evaluate baseline (6.4±6.1months since PD diagnosis) differences in pro-saccadic metrics between those with early PD and healthy age-matched adults; and 2) assess the ability of baseline pro-saccades to predict subsequent cognitive decline over 4.5 years.

Methods

One hundred and forty-one PD and 90 age-matched participants recruited at diagnosis underwent saccadometric assessment of pro-saccades at baseline and had cognition assessed at baseline, 18, 36 and 54-months. Pro-saccadic characteristics included latency, duration, amplitude, peak and average velocity. Cognitive assessment included executive function, attention, fluctuating attention and memory. Linear mixed-effects models examined pro-saccadic metrics as predictors of cognitive decline over 54-months.

Results

Pro-saccades were significantly impaired at baseline in PD compared with controls. Pro-saccadic characteristics of latency, duration, peak and average velocity predicted decline in global cognition, executive function, attention and memory over 54-months in PD. Additionally, only reduction in global cognition and attention were predicted by pro-saccadic metrics in age-matched adults, indicating that PD findings were not purely age-related.

Conclusion

Saccadic characteristics are impaired in early-PD and are predictive of cognitive decline in several domains. Assessment of saccades may provide a useful non-invasive biomarker for long-term PD cognitive decline in early disease.

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease (AD). Cognitive impairment is significant in PD, and cumulatively 80% may progress to dementia (PDD)[1]. Cognitive deficits significantly impact performance of daily activities, quality of life[2] and reduce life expectancy[3]. There is an urgent need to develop and examine biomarkers that can predict individuals at risk of cognitive decline in PD. Such biomarkers would optimize clinical management, assist in the development of effective or timely treatments, and allow sensitive monitoring of cognitive function. However, the underlying pathophysiology of cognitive decline in PD is complex and not fully understood, with contributions from dopaminergic and cholinergic dysfunction[4]. Additionally, cognitive functions are selectively impacted which leads to heterogeneous cognitive profiles[5]. Therefore, a single biomarker or predictive measure is unlikely to yield sufficient sensitivity, and a range of such markers is likely required. Clinical biomarkers may be important in PD, as laboratory or imaging biomarkers are complex, expensive and invasive[4].

Oculomotor dysfunction, such as saccadic (fast eye movement) impairment, occurs in PD and relates to cognitive function[6-9]. Saccadic impairments in PD vary depending on disease stage, but include hypometria (where a primary saccade undershoots a target and may be further impaired by PD pathology in the vertical rather than horizontal direction[11]), reduced amplitudes and increased latencies[8]. Due to their relationship with cognition, saccades may be a potential biomarker for those at risk of cognitive decline and PDD[6-9]. Saccades can be non-invasively measured using saccadometry, which is a simple and low-cost tool that can be used in clinical practice[10]. Saccadometry involves anti-saccade (voluntary) and pro-saccade (reflexive) paradigms[12], with greater errors made on such tasks by those with PD[8]. Anti-saccadic tasks require a voluntary saccade to be made in the opposite direction to a stimulus that appears on one side of a participant's view, whereas pro-saccades require a saccade to be made in the same direction as the stimulus appearance. Anti-saccades, therefore, require inhibition of a reflexive saccade towards the stimulus and voluntary saccade away from the stimulus. A growing body of evidence has demonstrated an association between the inability to inhibit reflexive saccades (i.e. anti-saccade error) and cognitive deficits[12]. Pro-saccade tasks require only a reflexive saccade towards the stimulus, and shorter latencies are related to anti-saccade errors and cognitive deficits[13]. However, pro-saccades have received less attention than anti-saccades despite their ease of application and similarities to usual neurological saccadic examination (i.e. looking towards a stimulus such as an examiner's fingers).

People with PD have shorter pro-saccade latencies with smaller amplitudes compared to controls[14], although in early-PD there have only been a few small studies with variable results reported[15-17]. Furthermore, reflexive saccades are useful in differential diagnosis, with minor impairments associated with isolated cortical (as in AD) or nigrostriatal (as in PD) neurodegeneration, and more pronounced deficits when pathology impacts both of these cortical and subcortical regions, as occurs in Dementia with Lewy Bodies (DLB) or PDD[18]. Additionally, deficits in dopaminergic (primarily voluntary, top-down, anti-saccades[19 20]) and cholinergic (primarily reflexive, bottom-up, pro-saccades[21-23]) innervation influences saccadic activity[24] and cognitive processes[25]. Despite these findings, the longitudinal relationship between saccades and cognition in PD is not established.

This study aimed to: 1) evaluate baseline differences in pro-saccadic metrics between those with early PD and healthy age-matched adults; and 2) assess the ability of pro-saccades recorded at baseline to predict subsequent cognitive decline over 4.5 years. We hypothesised

that discrete saccadic characteristics would be impaired at baseline in PD compared to controls, and that baseline pro-saccades would be sensitive to decline in selective cognitive functions in early PD.

Methods

Participants

Recently diagnosed people with idiopathic PD and healthy age-matched adults were recruited to the Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation-PD (ICICLE-PD) study at Newcastle. Participants were recruited between June 2009 and December 2011[26]. Idiopathic PD was diagnosed according to UK Queen Square Brain Bank criteria. Participants were assessed over four sessions; baseline, 18 months, 36 months and 54 months. Exclusion criteria included: cognitive impairment (≤24 Mini Mental State Exam [MMSE]), Dementia with Lewy Bodies, drug-induced parkinsonism, vascular parkinsonism, atypical parkinsonian syndromes, poor command of English language, and inability to give written, informed consent. Participants were assessed in an "on" motor state. The study was approved by the Newcastle and North Tyneside Research and Ethics Committee.

Clinical Assessment

Participant demographics including age (years), gender and years of education were recorded. Depression was assessed at each session using the Geriatric Depression Scale (GDS-15) and premorbid intelligence assessed at baseline using the National Adult Reading Test (NART). Parkinson's disease duration was recorded in months since diagnosis. Motor severity was assessed using the International Parkinson and Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part-III, Hoehn and Yahr Stage (H&Y) and levodopa equivalent daily dose (LEDD) was calculated[27]. As part of a full cranial nerve examination, visual acuity was assessed using a hand-held near-reading (40cm) Snellen chart reading card (normal was a minimum distance equivalent score of 20/40). We also recorded any anomalies in colour vision, accommodation and pupillary response, as well as the use of any visual aids by participants and any reports of diplopia.

Cognitive Assessment

A comprehensive cognitive assessment battery was completed at each visit (baseline, 18 months, 36 months and 54 months). Global cognition was measured using the Montreal Cognitive Assessment (MoCA)[28]. Executive function was measured using Cambridge Neuropsychological Test Automated Battery (CANTAB) one touch stockings (OTS) test, phonemic fluency (words beginning with F in 60 seconds) and semantic fluency (naming animals in 90 seconds)[29]. Attention was measured using Cognitive Drug Research battery (CDR)[30] simple reaction time (SRT), choice reaction time (CRT), and digit vigilance (DV) tests. Power of attention (PoA) was calculated as the mean reaction time (ms) of SRT, CRT and DV combined. Fluctuating attention (individual reaction time variability) was calculated as the coefficient of variance (CoV) of the SRT, CRT, and DV combined. Memory was measured using spatial recognition memory (SRM), pattern recognition memory (PRM), and paired associate learning (PAL) tests from CANTAB.

Saccadic Assessment

Saccades, specifically pro-saccades, were measured only at baseline using a standardized testing battery with a 'Saccadometer Advanced' device (1kHz; Ober Consulting, Poland; Figure 1)[31]. A detailed account of the saccadic assessment is provided as supplementary methods 1. Saccadic outcomes included mean and SD for Latency (i.e. reaction time),

Duration (i.e. time to completion), Amplitude (i.e. distance covered), Peak Velocity (i.e. maximum velocity value) and Average Velocity (i.e. mean of velocity across entire movement)[10].

Statistical Analysis

Statistical Analysis was conducted using SPSS (IBM Corp. v.21, USA) and R software (Version 3.0.1; R Foundation for Statistical Computing, Vienna, Austria). Data were examined for normality of distribution with visual histograms and Kolmogorov-Smirnov's test. Comparisons of means between two groups were performed using independent t-tests or Mann-Whitney U tests as appropriate. Ordinal data were compared using chi-squared tests. Associations between variables were examined using Pearson's or Spearman's correlations as appropriate. Within R, *lme4* was used to perform linear mixed effects analysis of the relationship between baseline saccadometry measures and cognition from baseline to 54 months. Due to the longitudinal nature of this study, there were some missing data (Supplementary Table 5). This form of multilevel modelling is suitable for longitudinal data analysis due to its ability to handle missing data[32], as it does not exclude subjects with missing data from the analysis. A random intercept model was used, where the intercept varied at the participant and time level. For each cognitive test, sex, number of years of completed education, age, time, medication (LEDD), depression (GDS-15) and disease severity (MDS-UPDRS III) were entered into the model as fixed effects, as well interactions of time with age (age x time), LEDD (LEDD x time), MDS-UPDRS III (MDS-UPDRS III x time) and depression (GDS-15 x time). A basic model for each cognitive test was produced by excluding non-significant predictors; saccadometry measures were then each added to the basic model. Each model fit was assessed by likelihood ratio tests and a stringent significance level of $p \leq 0.03$ was used due to the exploratory nature of the analysis.

Results

Participants

At baseline, a total of 141 PD participants and 90 age-matched controls completed clinical assessment, and were followed-up at 18-month intervals (Figure 2). PD participants had a mean disease duration of 6.4±6.1 months. A total of 86 PD and 62 healthy age-matched adult controls completed all assessments up to 54-months.

At baseline, there were no significant differences in the proportion of PD participants compared to controls in terms of abnormal visual acuity (44.7% vs. 68.9%, respectively, $p>0.05$) or diplopia (9.2% vs. 3.3%, respectively, $p>0.06$). A greater proportion of controls had corrected vision compared to PD participants (86.7% vs. 53.9%, respectively, $p<0.001$). PD participants were significantly impaired in all cognitive domains compared to controls (Table 1). PD participants also had significant impairments in baseline saccadic amplitude (p=.001) and Mean Velocity (p=.029) compared to age-matched adults. Weak but significant associations between baseline selective cognitive functions and saccadic metrics were observed for both groups, more so in PD (Supplementary Tables 1 and 2).

Many cognitive abilities declined across several domains in PD, and less so in age-matched adults over the course of the study (Supplementary Table 3). However, those with intact global cognition (MoCA≥26) did not show a significant change over time with repeated assessments, whereas those considered to have mild cognitive impairment (MCI) (MoCA <26) or who developed PDD (based on clinical diagnosis) declined over time[28].

Saccades predict cognitive decline over 54 months

Linear mixed effects models determined the association between declining cognition over 54 months and baseline saccadic metrics using all 141 PD participants (Table 2). The same analysis was performed in age-matched adults over 36 months, but associations with saccadometry measures were only found with declining MoCA and digit vigilance scores (Supplementary Table 4).

Global cognition

Baseline latency mean by time (χ^2=142.9, p<0.001), latency SD by time (χ^2=141.3, p<0.001) and baseline duration SD by time (χ^2=143.4, p<0.001) significantly improved the basic model and predicted decreasing MoCA score over 54 months. This indicated that shorter saccadic latency and more variable latency and duration at baseline predicted global cognitive decline in PD.

Executive function

Only baseline latency SD by time significantly predicted poorer OTS score and significantly improved the basic model (χ^2=150.6, p<0.001), indicating that greater saccadic latency variability was associated with decline in executive function in PD. However, saccadometry measures were not significant predictors of phonemic or semantic fluency (Table 2).

Attention

Some saccadometry measures were associated with PoA and PoA CoV as measures of attention, but not digit vigilance (Table 2). Increased baseline mean amplitude by time (χ^2=431.74, p<0.001), baseline peak velocity mean by time (χ^2=433.1, p<0.001) and baseline peak velocity SD by time (χ^2=430.0, p<0.001) were associated with lower PoA over 54 months. When comparing the three models, baseline peak velocity mean had the best predictive power (χ^2=1.3 and χ^2=6.2, respectively, p<0.001). Slower peak saccadic velocity at baseline therefore predicted decline in attention in PD.

Increased baseline mean duration by time was significantly associated with higher PoA CoV over 54 months and significantly improved the basic model (χ^2=237.5, p<0.001). Declining PoA CoV was predicted by lower baseline peak velocity SD by time (χ^2=235.1, p<0.001) and lower baseline average velocity mean by time (χ^2=240.1, p<0.001). Comparing the three models, baseline average velocity mean was the strongest model (χ^2=5.0 and χ^2=2.7, respectively, p<0.001). Slower average saccadic velocity at baseline, therefore, predicted decline in fluctuating attention in PD.

Memory

Baseline amplitude mean by time, peak velocity mean by time and average velocity mean by time significantly predicted change in PRM scores over 54 months (Table 2) and significantly improved the basic model (χ^2=145.6, χ^2=145.3 and χ^2=145.6, respectively, p<0.001 for all). No saccadometry measures were associated with SRM or PAL scores, although there was a trend (p=0.043, Table 2) observed for increased baseline latency mean by time improving the

model to predict worsening memory. Smaller saccadic amplitude, slower average velocity and shorter latency at baseline, therefore, predicted decline in memory in PD.

Discussion

To the best of our knowledge, this is the first study to examine pro-saccades in relation to cognitive decline in a large group of early PD participants and an age-matched control group. Our findings indicate that pro-saccades are impaired in early PD compared with age-matched controls, with deficits in amplitude and velocity. Furthermore, selective pro-saccade characteristics recorded at baseline can predict decline in various cognitive domains over the next 54 months in PD, whereas there is limited predictive capability for healthy age-matched adults.

Pro-saccades (reflexive saccades) were significantly shorter and slower at baseline in our early PD group (mean disease duration of six months) compared to healthy age-matched adults. Due to saccadic velocity calculation relying heavily on saccadic amplitude (i.e. velocity is amplitude divided by time) the deficits in amplitude likely account for the lower velocities found. In contrast, previous studies that have involved small numbers of PD participants have provided conflicting reports on whether reflexive saccades are impaired[15 16] or abnormal (i.e. increased velocity and latency)[17] in early PD. However, our findings suggest that saccades are impaired early in the disease. Although we did not find any relationship between levodopa dose and saccades within our study, pro-saccadic PD impairments may relate to levodopa medication intake, as previous studies have demonstrated that the use of dopaminergic medication can slow reflexive saccades in PD[33-35]. Dopaminergic therapies may impact reflexive saccadic function through improved or over-active saccadic inhibitory control of the pre-frontal cortex through dopaminergic circuits, as dopamine primarily underpins cognitive (voluntary, top-down) control of saccades[24 36]. Similarly, we found no relationship between pro-saccades and cholinergic medication burden (determined with the Anticholinergic Drug Scale), which was unsurprising as cholinergic therapies would likely increase rather than decrease reflexive saccade velocities through dampening saccadic inhibition[37]. Similarly, cholinergic therapies may also increase saccadic latency and reduce amplitude (or gain)[38]. Medication effect is one of the major challenges in interpretation of the results of saccadic impairments in PD, as it is difficult to determine whether deficits occur due to underlying PD pathology or the medications used to treat it. However, studies regarding the impact of medications on saccades are inconsistent and often conflicting, which may be a result of the small sample sizes examined. Despite potential medication effects, our results demonstrate that saccadometry is a sensitive tool to quantify impairments in early PD compared to those without PD.

Saccades predict decline in selective cognitive domains in PD

For PD participants, baseline pro-saccadic metrics independently predicted decline in cognitive outcomes over 54 months, specifically in global cognition, executive function, attention and memory. In contrast, pro-saccadic metrics only predicted decline in global cognition and attention in healthy age-matched adults over 36 months; this suggests that the associations found in PD subjects are not merely age-related. Specifically, greater saccadic duration variability (global cognition), latency variability (executive function), average and peak velocity (attention), and amplitude (memory) had the strongest predictive power for cognitive decline in PD across selective cognitive domains. These findings add to the literature pertaining to cross-sectional associations between saccades and cognition in PD and older

adults[39-41], which particularly link executive processes with voluntary saccades. Indeed, several previous cross-sectional studies have reported that cognitive impairment can be determined by examination of saccades in older adults[42 43], but the studies did not commonly assess reflexive saccades which limits comparisons to the current study.

The underlying pathophysiology involved in saccadic and cognitive impairment in PD is not fully understood and may vary among subjects[44 45]. The parietal cortex (posterior parietal cortex and parietal eye-field) and the brain stem cholinergic system rather than the dopaminergic reward system primarily elicit reflexive pro-saccades[24 36]. Saccadic latencies increase with anticholinergic medication and frontal lobe dysfunction is implicated in PD saccadic deficits, particularly as the disease progresses[8]. The cholinergic system also has a central role in cognition[46], particularly attention, and cholinergic deficits may therefore underpin both saccadic and cognitive dysfunction[47] in PD.

Study strengths and Limitations

A major strength of this study was the prospective design, examining a large cohort of recently diagnosed incident PD participants. Previous cross-sectional studies examining associations between saccades and cognition in PD have been limited by small sample sizes and disease heterogeneity, with little focus on long-term monitoring or comparison with age-matched controls.

Limitations included the inability of the saccadometry device to record vertical saccades, which may be prone to more significant impairment in PD, and therefore may be a more sensitive measure[48]. This study did not investigate anti-saccadic performance, which may strengthen longitudinal relationships between cognition and saccades due to the executive control required in performance. We also only assessed saccadic measures at baseline; future studies should consider repeating saccadic assessment concurrently with cognitive testing. We did not examine whether cognitive decline was better predicted with saccades or other potential clinical biomarkers, such as cognitive tests, which should be considered in future studies. As with many longitudinal studies, missing data were problematic (Supplementary Table 5). Additionally, the age-matched cohort completed detailed cognitive testing at 36-month follow up, but not at 54 months. However, utilising a linear mixed effect modelling approach facilitated statistical analysis despite missing data and does not remove participant data list-wise. Some participants improved in their neuropsychological assessment scores over time, which could be due to a learning effect, medication or normal fluctuations in cognition. To reduce practice effects, we used a time interval of 18 months between testing. Future studies could also stratify groups based on cognitive status (i.e. normal, MCI, PDD) to examine predictive power of saccades for cognitive decline within sub-groups. Finally, although visual abnormalities were screened for as part of a neurological examination, a detailed assessment of visual acuity or adoption of a more comprehensive ophthalmological battery were not undertaken in this cohort. Future studies should consider including such measures.

Conclusions

Saccades are a predictor of cognitive decline in PD, with selective relationships between saccade characteristics and cognitive domains. Our results provide evidence that quantitative saccadic analysis using saccadometry in early PD is a potentially useful predictive marker for cognitive decline. Saccadometry is a low-cost and easy to use tool, which allows

comprehensive saccadic analysis within clinical practice. Combining this assessment with other clinical tools and biomarkers may provide an optimal means of predicting cognitive decline and, ultimately, more targeted early therapeutic intervention for dementia. Future work will examine saccades as a predictor of PD dementia as the cohort evolves.

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Author roles

Samuel Stuart was involved with study design, data processing, statistical analysis, interpretation of data and drafted the manuscript. Rachael A. Lawson was involved with study design, coordination of the study, participant recruitment, data collection, statistical analysis, interpretation of data and drafted the manuscript. Jeremy Nell and Lisa Alcock were involved data processing and manuscript revision. Alison J Yarnall, Gordon W Duncan and Tien K Khoo were also involved with coordination of the study, participant recruitment, clinical assessment, data collection and manuscript revision. Roger A. Barker, Lynn Rochester and David J. Burn were principal investigators for the study, were involved with the study design and reviewed the manuscript.

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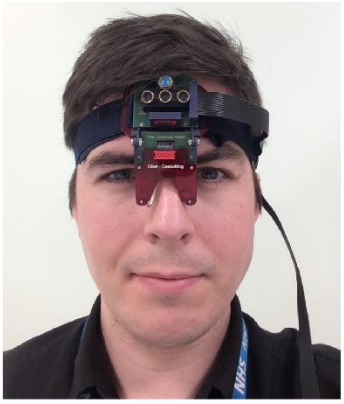
Hand-held Saccadometer Device



Saccadometer (front view)

Saccadometer (side view)

Figure 1 – Saccadometer device and placement.

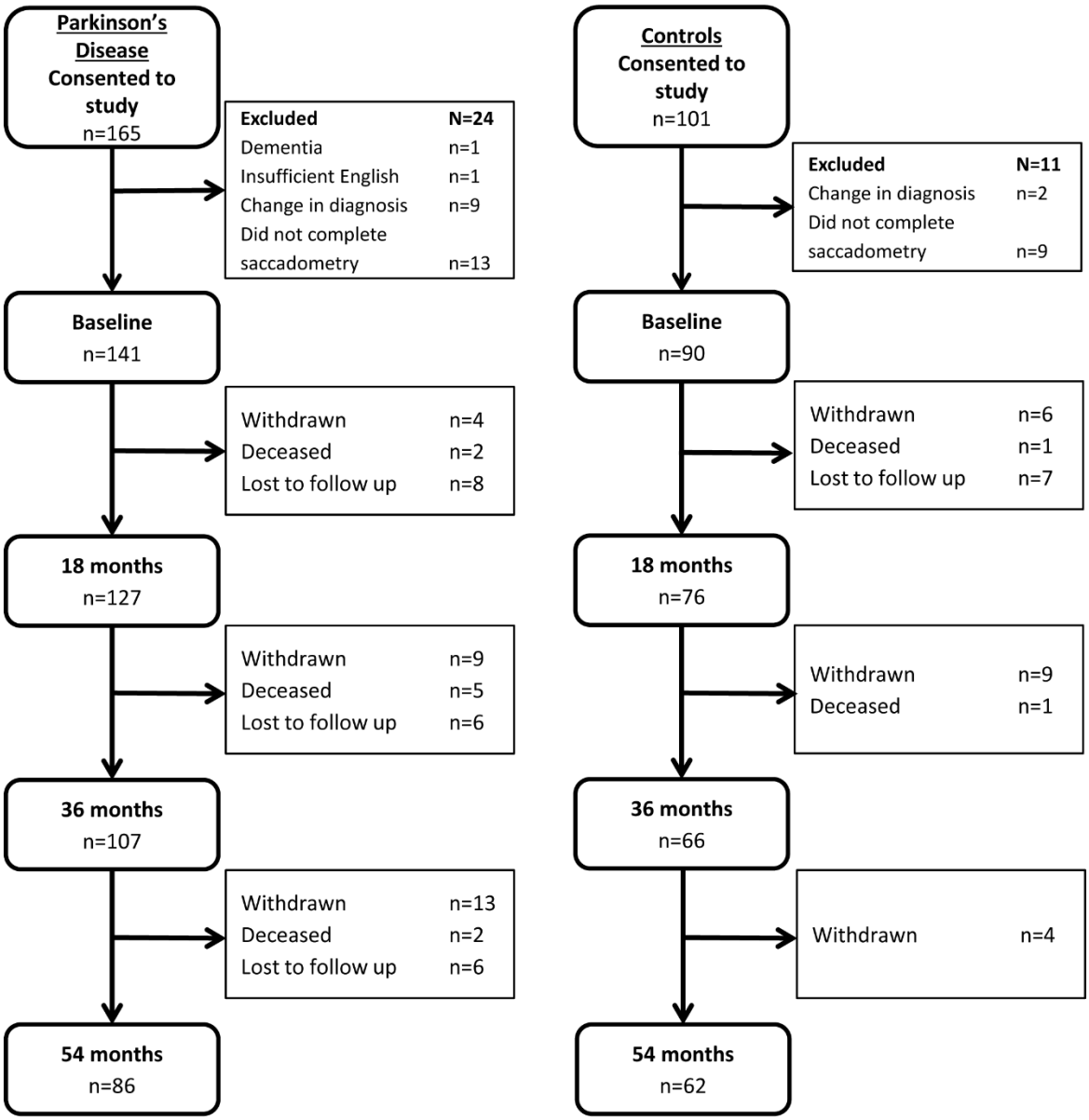


Figure 2 - Flowchart of participants recruited and assessed throughout the ICICLE-PD study.

Table 1 - Participant characteristics at baseline

Characteristics		**Control (n=90) Mean (SD)**	**PD (n=141) Mean (SD)**	***p***
Demographics				
	Age	67.9 (8.2)	66.4 (10.4)	.214
	Height	1.7 (0.1)	1.7 (0.1)	.878
	Weight	80.2 (14.2)	79.0 (16.5)	.565
	NART	115.9 (8.7)	114.7 (10.7)	.351
	GDS-15	1.0 (1.5)	2.8 (2.6)	**<.001**
	Years of Education	13.1 (3.4)	12.8 (3.8)	.521
Cognition				
Global	MoCA	26.9 (2.5)	25.3 (3.6)	**<.001**
	MMSE	29.0 (1.2)	28.6 (1.3)	**.023**
Executive function	Phonemic Fluency	12.5 (4.4)	11.0 (4.5)	**.001**
	Semantic Fluency	23.8 (6.1)	21.3 (6.5)	**.002**
	OTS	16.4 (2.6)	14.2 (4.0)	**.003**
Attention	PoA	1281.3 (139.1)	1370.5 (210.0)	**<.001**
	PoA CoV	50.2 (9.9)	53.2 (10.0)	.031
	Digit Vigilance	95.9 (5.8)	92.1 (12.5)	.055
Memory	PRM	20.7 (2.4)	19.7 (2.9)	.130
	SRM	16.1 (1.9)	15.3 (2.2)	.129
	PAL	1.8 (0.5)	2.1 (0.8)	**.001**
Clinical				
	Disease duration	-	6.4 (6.1)	-
	H&Y	-	I(32)/ II(80)/ III(28)/ IV(1)	-
	UPDRS III	-	26.9 (12.1)	-
	LEDD	-	178.1 (148.2)	-
Saccades				
	Latency - Mean	247.0 (60.1)	258.4 (64.3)	.180
	Latency - SD	150.5 (79.5)	168.9 (89.3)	.112
	Duration - Mean	53.2 (6.4)	52.1 (7.1)	.195
	Duration - SD	10.4 (5.5)	10.2 (5.0)	.882
	Amplitude - Mean	10.9 (2.0)	9.9 (2.2)	**.001**
	Amplitude - SD	2.7 (1.3)	2.7 (1.2)	.939
	Peak Vel - Mean	413.6 (96.9)	402.6 (108.6)	.438
	Peak Vel - SD	83.0 (47.2)	88.8 (49.8)	.377
	Av Vel - Mean	209.6 (46.8)	195.3 (49.2)	**.029**
	Av Vel - SD	46.2 (22.3)	45.5 (22.1)	.816

[Significance level p≤0.03 highlighted in bold. MoCA = Montreal Cognitive Assessment, MMSE = Mini Mental State Examination, OTS = One Touch Stockings, PoA = Power of attention, CoV = Coefficient of variance, PRM = Paired Recognition Memory, SRM = Spatial Recognition Memory, PAL = Paired Associated Learning, MDS-UPDRS III = Movement Disorders Society-Unified Parkinson's Disease Rating Scale Part III, LEDD = Levodopa equivalent daily dose, GDS-15 = Geriatric Depression Score, Vel = Velocity, SD = Standard Deviation. Saccadic latency and duration measured in milliseconds, Amplitude measured in degrees, Peak and Mean velocity measured in degrees per second]

Table 2: Summary of association between baseline pro-saccades and longitudinal cognitive scores using linear mixed effects modelling

		Global		Executive function						Attention						Memory					
		MocA[a]		Phonemic Fluency[b]		Semantic Fluency[c]		OTS[d]		PoA[e]		PoA CoV[f]		Digit Vigilance[g]		PRM[h]		SRM[i]		PAL[j]	
		β	p	β	p	β	p	β	p	β	p	β	p	β	p	β	p	β	p	β	p
Basic model + Latency Mean	Latency Mean	0.000	0.969	0.004	0.443	-0.002	0.824	-0.010	0.095	0.530	0.087	0.011	0.420	-0.016	0.357	-0.002	0.640	-0.005	0.031	0.000	0.898
	Latency Mean x Time	**-0.004**	**0.016**	-0.002	0.308	-0.003	0.404	0.004	0.128	0.142	0.285	0.004	0.540	-0.010	0.113	-0.003	0.060	0.003	0.043	0.001	0.414
Basic model + Latency SD	Latency Mean SD	0.001	0.872	0.004	0.263	-0.001	0.797	-0.007	0.099	0.352	0.112	0.007	0.456	-0.010	0.417	-0.002	0.350	-0.003	0.122	-0.001	0.593
	Latency Mean SD x Time	-0.002	0.032	-0.002	0.325	-0.003	0.148	**0.004**	**0.030**	0.069	0.448	0.005	0.275	-0.001	0.735	-0.001	0.251	0.001	0.282	0.000	0.641
Basic model + Duration Mean	Duration Mean	0.032	0.425	0.066	0.189	0.005	0.941	0.063	0.226	-0.942	0.731	-0.141	0.266	0.018	0.905	-0.015	0.663	0.008	0.703	-0.013	0.475
	Duration Mean x Time	-0.008	0.535	-0.007	0.703	0.001	0.967	-0.014	0.530	0.759	0.477	**0.128**	**0.018**	-0.023	0.648	-0.017	0.203	-0.025	0.069	0.014	0.219
Basic model + Duration SD	Duration SD	0.012	0.841	-0.076	0.280	-0.083	0.419	0.032	0.681	**9.507**	**0.017**	0.186	0.312	-0.295	0.196	-0.094	0.047	-0.037	0.247	-0.028	0.259
	Duration SD x Time	**-0.053**	**0.011**	-0.011	0.712	-0.059	0.171	-0.012	0.727	0.996	0.547	0.147	0.080	-0.055	0.498	-0.008	0.700	0.006	0.775	0.011	0.524
Basic model + Amplitude Mean	Amplitude Mean	-0.109	0.409	0.056	0.738	0.098	0.686	-0.073	0.662	-14.590	0.091	-0.449	0.265	0.694	0.153	-0.032	0.764	0.015	0.830	0.030	0.603
	Amplitude Mean x Time	0.076	0.079	0.082	0.159	0.064	0.457	0.028	0.691	-6.744	0.046	-0.275	0.113	0.180	0.279	**0.108**	**0.009**	-0.001	0.975	-0.021	0.572
Basic model + Amplitude SD	Amplitude SD	-0.156	0.518	-0.003	0.991	0.016	0.969	-0.323	0.295	-3.203	0.843	-0.232	0.756	0.500	0.579	-0.117	0.554	0.052	0.684	0.046	0.671
	Amplitude SD x Time	0.018	0.820	0.054	0.614	-0.072	0.645	0.206	0.114	-7.810	0.216	-0.267	0.406	0.301	0.329	0.116	0.128	-0.008	0.922	0.002	0.979
Basic model + Peak Vel Mean	Peak Vel Mean	-0.002	0.464	-0.002	0.569	0.002	0.709	-0.002	0.644	-0.205	0.239	-0.004	0.653	0.015	0.133	0.001	0.599	0.000	0.934	0.000	0.701
	Peak Vel Mean x Time	0.002	0.056	0.002	0.085	0.001	0.651	0.001	0.339	**-0.162**	**0.010**	**-0.008**	**0.018**	0.003	0.410	**0.002**	**0.029**	0.001	0.439	-0.001	0.362
Basic model + Peak Vel SD	Peak Vel SD	-0.002	0.720	-0.001	0.940	0.002	0.858	-0.002	0.808	-0.158	0.683	0.000	0.996	0.020	0.346	0.002	0.634	0.000	0.798	0.002	0.554
	Peak Vel SD x Time	0.002	0.194	0.003	0.325	0.000	0.992	0.005	0.100	**-0.380**	**0.009**	-0.012	0.107	0.010	0.172	0.003	0.108	0.001	0.757	-0.001	0.578
Basic model + Av Vel Mean	Average Vel Mean	-0.006	0.315	-0.003	0.699	0.003	0.783	-0.005	0.515	-0.443	0.254	-0.008	0.655	0.025	0.254	0.001	0.909	0.000	0.885	0.002	0.523
	Average Vel Mean x Time	0.003	0.127	0.004	0.159	0.002	0.645	0.001	0.718	-0.297	0.044	**-0.018**	**0.020**	0.007	0.338	**0.004**	**0.014**	0.002	0.376	-0.002	0.329
Basic model + Av Vel SD	Average Vel SD	-0.008	0.563	-0.008	0.624	0.002	0.932	-0.006	0.718	-0.309	0.723	0.002	0.969	0.037	0.442	-0.001	0.903	0.000	0.9871	0.003	0.617
	Average Vel SD x Time	0.003	0.429	0.006	0.314	0.001	0.929	0.009	0.227	-0.729	0.035	-0.029	0.108	0.024	0.161	0.007	0.108	0.002	0.6767	-0.001	0.708

Significant results p ≤0.03 highlighted in bold.

Supplementary Material: Detailed Saccadic Assessment

Saccadometry allows for up to 300 saccades to be recorded within 15 minutes, and is automatically calibrated using a small number (n=20) of preliminary trials. Specifically, participants looked at peripheral targets 10° to the left and 10° to the right of the central target. Targets were projected on an even surfaced wall at a distance of 1.5m from the participants chair in a quiet room with dimmed lights. Those with visual correction via contact lenses wore these during testing, but those who required glasses were asked during calibration if they could see all three saccadic targets clearly without their glasses and without diplopia before testing. Prior to the data recording, an interactive tutorial was given to each participant on the testing procedures. Each participant reported seeing all three target lights clearly, and demonstrated full understanding of the expected pro-saccade task before data recording.

The saccadometer consisted of a head-mounted sensor that rested on the nose of the participant and measured horizontal saccades. The saccadometry task involved a pro-saccadic step task paradigm with no anti-saccadic gap or overlap of stimuli. The saccadometer directed a laser (Red dot; 13 cd/m2, ~ 0.1°) at a wall 1.5m in front of the participant that they were instructed to fixate on. After a fixed fore-period (1 sec) and then a random fore-period (0.5-1sec) the central fixation light was extinguished and either a left or right target, chosen at random (50% fixed probability), was turned on and remained until a saccade was performed or for a maximum of two seconds. Participants performed a single run of the pro-saccade task for a total of 90 saccades (or trials) which took 5-10 minutes. Metrics from these responsive pro-saccades were extracted for further analysis.

Recordings were stored initially in the saccadometer control unit before being transferred to LatencyMeter software (v.6.6, Ober Consulting). The LatencyMeter program automatically detected saccades via a velocity threshold (>5°/s) and removed erroneous trials due to blinks, as well as abnormal profiles (i.e. eye movement falling outside of normal range) as determined by the velocity, acceleration, duration and position (i.e. wrong direction) of eye movement traces[1]. It removed eye movements falling outside of an amplitude range (5-15°) and latency range 50-600ms (arbitrary limits were chosen to exclude anticipatory saccades or those with prolonged latency due to inattention, but to include express or other early saccades)[1]. Trial removal was based on the log likelihood value for each sample of a given trace according to the mean and standard deviation (SD) calculated from the whole population of traces for that sample[1]. The trace was rejected if the average log likelihood value for whole trace was below the rejection threshold for the profile metrics[1]. Other criteria for rejection were saccade detection failure and sensor range saturation. All pro-saccadic signals were visually checked via graphed traces of eye location and velocity to ensure appropriate recording using the LatencyMeter software.

References

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Supplementary Table 1 - Correlations between baseline cognition and saccadometry metrics in Parkinson's disease

r(p)	Global	Executive function				Attention		Memory		
	MocA	**Phonemic Fluency**	**Semantic Fluency**	**OTS**	**PoA**	**PoA CoV**	**Digit Vigilance**	**PRM**	**SRM**	**PAL**
Latency Mean	-.116 (.191)	.056 (.507)	-.161 (.059)	***-.263 (.002)***	***.186 (.026)***	.061 (.470)	-.116 (.168)	-.097 (.263)	***-.285 (.001)***	***.321 (<.001)***
Latency SD	-.025 (.779)	.120 (.154)	-.067 (.438)	***-.203 (.018)***	.118 (.159)	.067 (.429)	-.090 (.285)	-.054 (.535)	***-.239 (.005)***	***.253 (.003)***
Duration Mean	.041 (.643)	.119 (.157)	-.034 (.689)	.110 (.203)	.046 (.588)	-.119 (.157)	-.049 (.560)	.008 (.929)	.011 (.899)	-.170 (.047)
Duration SD	-.015 (.867)	-.070 (.408)	-.057 (.504)	.025 (.770)	***.308 (<.001)***	.128 (.127)	-.163 (.052)	-.085 (.326)	***-.195 (.023)***	.017 (.848)
Amplitude Mean	-.116 (.193)	.053 (.532)	.029 (.739)	-.021 (.812)	***-.190 (.023)***	-.054 (.525)	.162 (.054)	-.059 (.497)	.047 (.588)	-.042 (.624)
Amplitude SD	-.137 (.122)	.014 (.864)	-.026 (.759)	-.081 (.351)	.017 (.843)	.042 (.618)	.046 (.588)	-.058 (.506)	-.028 (.743)	.089 (.301)
Peak Vel Mean	-.094 (.293)	-.047 (.577)	.031 (.714)	-.047 (.585)	-.147 (.080)	.025 (.765)	***.186 (.026)***	-.015 (.865)	.027 (.754)	.029 (.740)
Peak Vel SD	-.067 (.454)	.021 (.802)	.011 (.900)	-.029 (.742)	-.017 (.839)	.107 (.202)	.111 (.186)	-.001 (.994)	.013 (.880)	.075 (.387)
Av Vel Mean	-.125 (.161)	-.026 (.757)	.035 (.681)	-.051 (.552)	-.166 (.047)	.021 (.801)	.154 (.067)	-.041 (.637)	.022 (.802)	.046 (.595)
Av Vel SD	-.119 (.180)	-.025 (.768)	-.012 (.890)	-.029 (.733)	-.027 (.747)	.087 (.303)	.090 (.284)	-.031 (.717)	-.018 (.831)	.075 (.386)

Figures in table are Pearson's r (p-value); Significant p ≤0.03 results highlighted in bold.

MoCA = Montreal Cognitive Assessment, OTS = One Touch Stockings, PoA = Power of attention, CoV = Coefficient of variance, PRM = Paired Recognition Memory, SRM = Spatial Recognition Memory, PAL = Paired Associated Learning, MDS-UPDRS III = Movement Disorders Society-Unified Parkinson's Disease Rating Scale Part III, LEDD = Levodopa equivalent daily dose, GDS-15 = Geriatric Depression Score.

Supplementary Table 2 - Correlations between baseline cognition and saccadometry metrics in controls

r(p)	Global	Executive function			Attention			Memory		
	MocA	**Phonemic Fluency**	**Semantic Fluency**	**OTS**	**PoA**	**PoA CoV**	**Digit Vigilance**	**PRM**	**SRM**	**PAL**
Latency Mean	-.182 (.087)	.012 (.912)	-.147 (.166)	***-.324 (.002)***	.209 (.054)	.177 (.102)	-.107 (.326)	-.111 (.311)	-.015 (.890)	.224 (.039)
Latency SD	-.024 (.826)	.136 (.200)	-.108 (.312)	***-.290 (.007)***	.222 (.040)	.183 (.091)	-.076 (.486)	-.044 (.686)	.095 (.389)	.157 (.150)
Duration Mean	-.032 (.769)	.022 (.834)	.100 (.350)	.002 (.986)	.109 (.319)	-.003 (.980)	-.053 (.629)	-.161 (.141)	-.032 (.770)	-.027 (.807)
Duration SD	.098 (.362)	.065 (.544)	.132 (.216)	-.091 (.408)	.177 (.104)	-.101 (.357)	.007 (.947)	-.055 (.616)	.126 (.250)	-.120 (.276)
Amplitude Mean	-.168 (.116)	-.100 (.351)	-.089 (.406)	-.177 (.105)	.028 (.798)	.066 (.548)	-.023 (.837)	.105 (.341)	.153 (.163)	.020 (.855)
Amplitude SD	-.062 (.562)	.061 (.567)	.093 (.382)	-.162 (.140)	.095 (.387)	.073 (.504)	-.048 (.658)	.182 (.095)	.234 (.031)	-.035 (.749)
Peak Vel Mean	-.145 (.174)	-.110 (.303)	-.118 (.267)	-.164 (.134)	.015 (.890)	.011 (.923)	.022 (.837)	.166 (.129)	.167 (.127)	.018 (.867)
Peak Vel SD	-.044 (.679)	-.046 (.669)	.029 (.784)	-.084 (.446)	.077 (.478)	.039 (.720)	-.014 (.897)	.188 (.084)	.224 (.039)	-.033 (.764)
Av Vel Mean	-.121 (.259)	-.118 (.267)	-.112 (.294)	-.163 (.137)	-.029 (.794)	.039 (.723)	-.005 (.965)	.153 (.162)	.147 (.178)	.028 (.798)
Av Vel SD	-.019 (.860)	-.034 (.747)	.120 (.262)	-.091 (.410)	-.004 (.971)	-.017 (.875)	.001 (.993)	.225 (.038)	***.247 (.023)***	-.073 (.505)

Figures in table are Pearson's r (p-value); Significant p≤0.03 results highlighted in bold.

MoCA = Montreal Cognitive Assessment, OTS = One Touch Stockings, PoA = Power of attention, CoV = Coefficient of variance, PRM = Paired Recognition Memory, SRM = Spatial Recognition Memory, PAL = Paired Associated Learning, MDS-UPDRS III = Movement Disorders Society-Unified Parkinson's Disease Rating Scale Part III, LEDD = Levodopa equivalent daily dose, GDS-15 = Geriatric Depression Score.

Supplementary Table 3 - Cognitive change over 36 months

	Baseline (A1)				18months (A2)				36months (A3)				Paired change (A3-A1)				Repeated measures (A1, A2, A3)			
	Control (n=90)		PD (n=141)		Control (n=76)		PD (n=127)		Control (n=66)		PD (n=107)		Control		PD		Control		PD	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Chi sq	p	Chi sq	p
MoCA	26.9	2.5	25.3	3.6	27.4	2.6	25.8	3.8	27.2	2.8	25.6	4.0	-0.19	2.45	-0.28	2.85	3.9	0.137	7.8	**0.020**
F	12.5	4.4	11.0	4.5	12.8	3.8	12.1	4.4	13.1	4.2	12.7	4.9	-0.71	3.61	-1.49	4.12	4.9	0.086	10.0	**0.007**
Animals	23.8	6.1	21.3	6.5	23.4	7.1	21.6	7.1	23.2	5.6	21.3	7.9	1.02	5.83	0.55	6.59	1.2	0.543	4.7	0.096
OTS	16.4	2.6	14.2	4.0	16.5	2.5	14.1	4.6	16.4	2.6	12.5	6.0	0.31	2.32	1.92	4.58	0.2	0.901	11.1	**0.004**
PoA	1281.3	139.1	1370.5	210.0	1306.6	161.0	1415.7	224.5	1333.0	185.1	1466.8	304.3	-60.78	139.58	-117.65	253.71	5.3	0.069	33.7	**0.000**
PoA CoV	50.2	9.9	53.2	10.0	51.9	8.8	55.2	12.7	53.7	13.9	57.1	13.3	-3.96	13.14	-3.98	11.01	4.9	0.086	14.8	**0.001**
Digit Vig	95.9	5.8	92.1	12.5	96.5	6.7	89.9	14.5	95.0	12.9	89.3	14.0	0.49	11.93	3.64	10.35	5.9	0.051	4.8	0.091
PRM	20.7	2.4	19.7	2.9	20.7	2.6	19.8	2.9	20.6	2.9	19.6	3.5	0.05	2.28	0.40	2.50	0.2	0.888	1.5	0.478
SRM	16.1	1.9	15.3	2.2	1.9	0.6	2.3	1.0	15.4	2.3	5.8	2.4	1.07	2.11	9.85	3.79	103.5	**0.000**	187.6	**0.000**
PAL	1.8	0.5	2.1	0.8	15.6	2.1	14.5	2.8	1.9	0.7	2.3	1.1	-0.11	0.53	-0.30	0.77	93.0	**0.000**	151.9	**0.000**

[Significance level p ≤ 0.03 highlighted in bold]

Supplementary Table 4 - Summary of the association between baseline saccadometry measures and longitudinal cognitive scores using linear mixed effects modelling in controls

		Global		Executive function						Attention						Memory					
		MocA[a]		Phonemic Fluency[b]		Semantic Fluency[c]		OTS[d]		PoA[e]		PoA CV[f]		Digit Vigilance[g]		PRM[h]		SRM[i]		PAL[j]	
		β	p	β	p	β	p	β	p	β	p	β	p	β	p	β	p	β	p	β	p
Basic model + Latency Mean	Latency Mean	0.000	0.984	-0.001	0.924	-0.006	0.521	-0.012	**0.007**	0.293	0.267	0.008	0.660	-0.007	0.603	0.002	0.728	0.001	0.630	-0.001	0.762
	Latency Mean x Time	-0.002	0.397	0.000	0.968	-0.006	0.280	0.004	0.089	0.024	0.858	0.004	0.718	0.014	0.097	0.000	0.862	0.000	0.868	0.001	0.611
Basic model + Latency SD	Latency Mean SD	0.002	0.526	0.007	0.174	-0.005	0.489	-0.007	0.025	0.351	0.069	0.015	0.237	-0.004	0.679	0.001	0.772	0.003	0.195	0.000	0.949
	Latency Mean SD x Time	-0.001	0.649	-0.002	0.417	-0.003	0.396	0.003	0.173	-0.072	0.483	-0.004	0.615	**0.016**	**0.010**	0.002	0.361	-0.001	0.605	0.001	0.678
Basic model + Duration Mean	Duration Mean	-0.004	0.919	0.001	0.991	0.128	0.152	0.015	0.707	1.827	0.450	-0.045	0.778	-0.035	0.786	-0.048	0.211	-0.001	0.962	-0.014	0.496
	Duration Mean x Time	-0.028	0.209	-0.050	0.137	-0.084	0.098	-0.010	0.692	-0.862	0.513	0.061	0.562	-0.034	0.669	0.014	0.571	0.006	0.793	0.008	0.614
Basic model + Duration SD	Duration SD	0.019	0.673	0.062	0.436	0.093	0.385	-0.039	0.416	5.447	0.059	-0.060	0.749	-0.050	0.738	-0.041	0.363	0.040	0.196	-0.008	0.716
	Duration SD x Time	-0.031	0.240	-0.037	0.349	-0.115	0.057	0.013	0.647	-2.782	0.071	-0.112	0.358	0.086	0.371	0.020	0.471	-0.031	0.218	0.019	0.316
Basic model + Amplitude Mean	Amplitude Mean	-0.178	0.155	-0.200	0.352	-0.326	0.251	-0.278	0.035	2.831	0.714	0.259	0.604	-0.038	0.925	0.080	0.523	0.078	0.369	-0.029	0.663
	Amplitude Mean x Time	**0.171**	**0.018**	0.071	0.502	0.013	0.933	0.074	0.335	6.560	0.109	0.344	0.282	0.207	0.409	-0.038	0.605	0.026	0.699	-0.013	0.801
Basic model + Amplitude SD	Amplitude SD	-0.102	0.603	0.276	0.405	0.371	0.399	-0.385	0.061	8.705	0.454	0.582	0.450	-0.219	0.722	0.309	0.109	0.231	0.088	0.018	0.861
	Amplitude SD x Time	0.193	0.098	0.009	0.958	-0.353	0.152	0.132	0.271	4.967	0.438	-0.096	0.847	0.419	0.283	-0.035	0.760	-0.050	0.634	0.003	0.969
Basic model + Peak Vel Mean	Peak Vel Mean	-0.004	0.165	-0.004	0.387	-0.010	0.095	-0.006	0.040	0.072	0.654	0.001	0.900	0.001	0.900	0.003	0.181	0.002	0.315	0.000	0.907
	Peak Vel Mean x Time	**0.004**	**0.003**	0.003	0.137	0.001	0.803	0.002	0.242	0.120	0.165	0.000	0.970	0.007	0.191	-0.001	0.651	0.000	0.929	0.000	0.818
Basic model + Peak Vel SD	Peak Vel SD	-0.004	0.485	-0.002	0.825	0.001	0.919	-0.007	0.248	0.270	0.399	0.010	0.650	-0.002	0.902	0.009	0.086	0.006	0.107	0.000	0.944
	Peak Vel SD x Time	0.007	0.047	0.005	0.236	-0.004	0.511	0.001	0.860	0.165	0.337	-0.011	0.421	0.015	0.143	0.000	0.891	-0.002	0.560	0.000	0.964
Basic model + Mean Vel Mean	Average Vel Mean	-0.007	0.180	-0.009	0.316	-0.020	0.107	-0.012	0.036	-0.008	0.980	0.011	0.608	-0.002	0.931	0.005	0.342	0.003	0.388	0.000	0.899
	Average Vel Mean x Time	**0.009**	**0.005**	0.006	0.167	0.005	0.447	0.003	0.337	0.290	0.103	0.007	0.596	0.012	0.268	-0.002	0.455	0.000	0.974	-0.001	0.653
Basic model + Mean Vel SD	Average Vel SD	-0.012	0.315	-0.001	0.940	0.017	0.526	-0.020	0.098	0.181	0.793	0.013	0.782	-0.008	0.817	0.018	0.112	0.012	0.116	-0.003	0.642
	Average Vel SD x Time	**0.018**	**0.009**	0.008	0.374	-0.016	0.264	0.007	0.315	0.328	0.370	0.000	0.994	0.027	0.229	0.000	0.976	0.000	0.940	-0.001	0.860

Significant results p ≤0.03 highlighted in bold

a Basic model = age, MDS-UPDRS III, Time; b Basic model = Number of years of education, age, time, age x time; c Basic model = Sex, number of years of education, age, LEDD, time; d Basic model = Age, time, MDS-UPDRS III, age x time, MDS-UPDRS III x time; e Basic model = Age, time, MDS-UPDRS III, GDS-15, age x time, MDS-UPDRS III x time, GDS-15 x time; f Basic model = Number of years of education, age, time, MDS-UPDRS III; g Basic model = Age, time, LEDD, MDS-UPDRS III, GDS-15, Age x time, LEDD x time, MDS-UPDRS III x time; h Basic model = Number of years of education, age, GDS-15, time; i Basic model = MDS-UPDRS III, time, MDS-UPDRS III x time; j Basic model = Time.

Supplementary Table 5 - Missing cognitive data

		MoCA	F	Animals	OTS	PoA	PoA CoV	Digit Vig	PRM	SRM	PAL
PD											
	Baseline (n=141)	13 Introduced later in study	1 Missing data	1 Missing data	7 Visual impairment (n=2), Missing data (n=5)	2 Equipment failure	2 Equipment failure	2 Equipment failure	7 Visual impairment (n=2), Missing data (n=5)	7 Visual impairment (n=2), Missing data (n=5)	7 Visual impairment (n=2), Missing data (n=5)
	18 months (n=127)	0	0	0	3 Visual impairment (n=2), Missing data (n=1)	3 Equipment failure	3 Equipment failure	3 Equipment failure	3 Visual impairment (n=2), Missing data (n=1)	3 Visual impairment (n=2), Missing data (n=1)	3 Visual impairment (n=2), Missing data (n=1)
	36 months (n=107)	3 Missing data	1 Missing data	1 Missing data	5 Visual impairment (n=2), Missing data (n=3)	3 Missing data	3 Missing data	3 Missing data	5 Visual impairment (n=2), Missing data (n=3)	5 Visual impairment (n=2), Missing data (n=3)	5 Visual impairment (n=2), Missing data (n=3)
	54 months (n=86)	0	0	0	36 Change in protocol, not completed (n=36), Visual impairment (n=1)	35 Change in protocol, not completed	35 Change in protocol, not completed	35 Change in protocol, not completed	36 Change in protocol, not completed (n=36), Visual impairment (n=1)	36 Change in protocol, not completed (n=36), Visual impairment (n=1)	36 Change in protocol, not completed (n=36), Visual impairment (n=1)
Control											
	Baseline (n=90)	1 Missing data	0	0	5 missing data	4 Equipment failure (n=3), Missing data (n=1)	4 Equipment failure (n=3), Missing data (n=1)	4 Equipment failure (n=3), Missing data (n=1)	5 missing data	5 missing data	5 missing data
	18 months (n=76)	**2**	0	0	0	1 Missing data	1 Missing data	1 Missing data	0	0	0
	36 months (n=66)	1 Missing data	1 Missing data	1 Missing data	2 Missing data	1 Missing data	1 Missing data	1 Missing data	2 Missing data	2 Missing data	2 Missing data
	54 months (n=62)	0	0	0	Change in protocol, not completed	Change in protocol, not completed	Change in protocol, not completed	Change in protocol, not completed	Change in protocol, not completed	Change in protocol, not completed	Change in protocol, not completed